US006548494B1

(12) **United States Patent**
Webber et al.

(10) **Patent No.: US 6,548,494 B1**
(45) **Date of Patent: Apr. 15, 2003**

(54) **TRICYCLIC INHIBITORS OF POLY(ADP-RIBOSE) POLYMERASES**

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(73) Assignee: **Agouron Pharmaceuticals, Inc.**, San Diego, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/653,184**

(22) Filed: **Aug. 31, 2000**

Related U.S. Application Data

(60) Provisional application No. 60/152,142, filed on Aug. 31, 1999.

(51) **Int. Cl.**[7] **C07D 487/06**; A61K 31/5517; A61P 35/00

(52) **U.S. Cl.** **514/220**; 540/496; 540/499

(58) **Field of Search** 540/496, 499; 514/220

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WO	WO 95/26186	10/1995
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WO	WO 98/33802	8/1998
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WO	WO 98/51308	11/1998
WO	WO 99/11622	3/1999
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Choi, D., "At the scene of ischemic brain injury: Is PARP a perp?", *Nature Medicine 3(10)*, 1073–1074 (1997).
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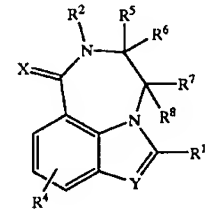
Primary Examiner—Bruck Kifle
(74) *Attorney, Agent, or Firm*—Karl Neidert; Bryan C. Zielinski; Peter Richardson

(57) **ABSTRACT**

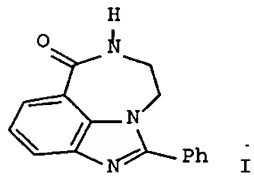
Compounds of the formula shown below are poly(ADP-ribosyl)transferase inhibitors:



Such compounds are useful as therapeutics in treating cancers and in ameliorating the effects of stroke, head trauma, and neurodegenerative disease.

13 Claims, No Drawings

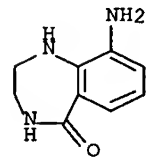
L4 ANSWER 1 OF 12 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2002:954525 CAPLUS
DN 138:170205
TI Tricyclic Benzimidazoles as Potent Poly(ADP-ribose) Polymerase-1 Inhibitors
AU Skalitzky, Donald J.; Marakovits, Joseph T.; Maegley, Karen A.; Ekker, Anne; Yu, Xiao-Hong; Hostomsky, Zdenek; Webber, Stephen E.; Eastman, Brian W.; Almassy, Robert; Li, Jianke; Curtin, Nicola J.; Newell, David R.; Calvert, A. Hilary; Griffin, Roger J.; Golding, Bernard T.
CS Pfizer Global R&D, La Jolla/Agouron Pharmaceuticals Inc., San Diego, CA, 92121, USA
SO Journal of Medicinal Chemistry (2003), 46(2), 210-213
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
OS CASREACT 138:170205
GI



I

AB Novel tricyclic benzimidazole carboxamide poly(ADP-ribose) polymerase-1 (PARP-1) inhibitors, e.g., I, have been synthesized. Several compds. were found to be powerful chemopotentiators of temozolomide and topotecan in both A549 and LoVo cell lines. In vitro inhibition of PARP-1 was confirmed by direct measurement of NAD+ depletion and ADP-ribose polymer formation caused by chem. induced DNA damage.

IT **328546-66-3P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)(prepn. of intermediate aminobenzodiazepinone via cyclization of nitrobromobenzoic acid Me ester with ethylene diamine and subsequent redn.)
RN 328546-66-3 CAPLUS
CN 5H-1,4-Benzodiazepin-5-one, 9-amino-1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



RE.CNT 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 12 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2002:428911 CAPLUS
DN 137:6205
TI Preparation of benzazepinones, isoquinolinones and related compounds as inhibitors of poly(ADP-ribose) polymerase (PARP) for the prevention and/or treatment of tissue damage from cell trauma or cell death due to necrosis or apoptosis.
IN Ferraris, Dana V.; Li, Jia-He; Kalish, Vincent J.; Zhang, Jie
PA Guilford Pharmaceuticals Inc., USA
SO PCT Int. Appl., 152 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

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	US 2003022883	A1	20030130	US 2001-996776	20011130
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OS MARPAT 137:6205
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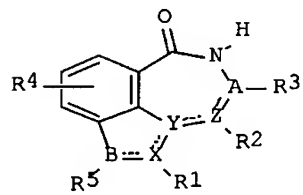

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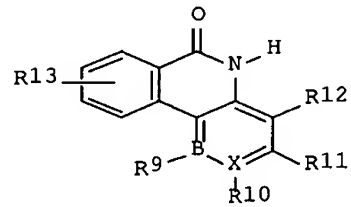

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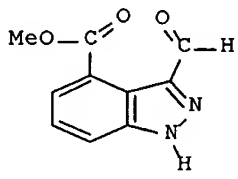
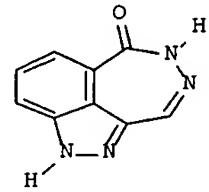


III



IV

AB This invention discloses the prepn. of title compds. I and II, their pharmaceutically acceptable salts, and related compds. as inhibitors of poly(ADP-ribose) polymerase (PARP) [wherein: A = N, C, CH2, CH; B = C, N,

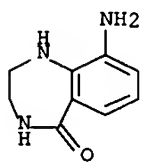
NH, S, SO, SO2; X = C, CH, N; Y = C, N; Z = C, CH2, N, CO; provided that at least one of X, Y, or Z is N; R1, R2, R3, R5 when present are optionally or independently = H, OH, :O, (un)substituted alkyl, alkenyl, alkynyl, alkoxy, carboxy, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, halogen, amine, COR8 (R8 = H, OH, (un)substituted alkyl, alkenyl, alkynyl, alkoxy, carboxy, cycloalkyl, heterocycloalkyl, aryl, heteroaryl), OR6, NR6R7 (R6, R7 independently = H, (un)substituted alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl); R1, R2, R3, R5 optionally form ring through a straight or branched C1-4alkyl which may addnl. contain 1-2 double or triple bonds; R4 = 1-3 of H, halo, or alkyl; with proviso that when A, X, or Z = C, then R1, R2, R3 when present may also independently = halogen, CN, O; R9, R10, R11, R12 optionally or independently = H, halogen, amino, OH, halo-amine, O-alkyl, O-aryl, (un)substituted alkyl, alkenyl, alkynyl, alkoxy, carboxy, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, COR8; R13 = 1-3 of H, halogen, alkoxy, alkyl]. For example, cyclocondensation of formylindazole III (prepd. from Me indole-4-carboxylate and NaNO2/AcOH), with hydrazine provided claimed benzoazulenone IV as a white solid. Benzoazulenone IV inhibited human recombinant PARP at an IC50 of 0.018 .mu.M. PARP IC50 inhibition studies for an addnl. 156 examples are provided, ranging in values from 0.01 to 20 .mu.M. Biol. data are provided for the in vivo treatment of focal cerebral ischemia and gout via PARP inhibition with selected compds. II. The present invention is believed to protect cells, tissue and organs against the ill-effects of reactive free radicals and nitric oxide through inhibition of PARP activity.

IT **328546-66-3P**

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT(Reactant or reagent)(intermediate; prepn. of benzazepinones, isoquinolinones and related compds. as inhibitors of poly(ADP-ribose) polymerase (PARP))

RN 328546-66-3 CAPLUS

CN 5H-1,4-Benzodiazepin-5-one, 9-amino-1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



L4 ANSWER 3 OF 12 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2001:225212 CAPLUS
DN 134:266331
TI Preparation of 2-phenyl-5,6-dihydro-imidazo[4,5,1-jk][1,4]benzodiazepin-7(4H)-ones as poly(ADP ribose) polymerase inhibitors.
IN Lubisch, Wilfried; Kock, Michael; Hoeger, Thomas; Grandel, Roland; Mueller, Reinhold; Schult, Sabine
PA BASF A.-G., Germany
SO Ger. Offen., 12 pp.
CODEN: GWXXBX
DT Patent
LA German
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	DE 19946289	A1	20010329	DE 1999-19946289	19990928
	WO 2001023386	A2	20010405	WO 2000-EP9023	20000915
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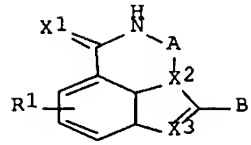
OS MARPAT 134:266331
GI



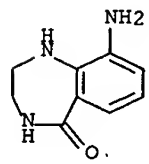
I

AB Title compds. [I; A = (substituted) C1-3 alkylene; X1 = S, O, NE; X2 = N, (substituted) C; X3 = N, CR2; R2 = H, alkyl, alkylphenyl, Ph; R1 = H, halo, OH, NO2, CF3, cyano, alkyl, alkoxy, etc.; B = (unsatd.) (O-, N-, S-interrupted) (substituted) mono-, bi-, tricyclyl] were prepd. as poly(ADP ribose) polymerase inhibitors (no data). Thus, Me 2-chloro-3-nitrobenzoate was heated with K2CO3 and H2NCH2CH2NH2 in DMF for 3 at 120.degree. to give 9-nitro-1,2,3,4-tetrahydro-5H-1,4-benzodiazepin-5-one, which was hydrogenated using Pd/C in EtOH to give 9-amino-1,2,3,4-tetrahydro-5H-1,4-benzodiazepin-5-one. The latter in MeOH contg. HOAc was treated dropwise with 4-(4-methylpiperazin-1-yl)benzaldehyde in MeOH followed by 1 h stirring at room temp.; Cu(OAc)2, Na2S, and HCl in H2O were added followed by 30 min reflux to give 2-[4-(4-methylpiperazin-1-yl)phenyl]-5,6-dihydro-imidazo[4,5,1-jk][1,4]benzodiazepin-7(4H)-one.

IT **328546-66-3P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of phenyldihydroimidazobenzodiazepinones as PARP inhibitors)

RN 328546-66-3 CAPLUS

CN 5H-1,4-Benzodiazepin-5-one, 9-amino-1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



L4 ANSWER 4 OF 12 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2001:167995 CAPLUS
DN 134:207833
TI Preparation of tricyclic inhibitors of poly(ADP-ribose) polymerases
IN Webber, Stephen Evan; Skalitzky, Donald James; Tikhe, Jayashree Girish; Kumpf, Robert Arnold; Marakovits, Joseph Timothy; Eastman, Walter Brian
PA Agouron Pharmaceuticals, Inc., USA; Cancer Research Campaign Technology Limited
SO PCT Int. Appl., 236 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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OS MARPAT 134:207833
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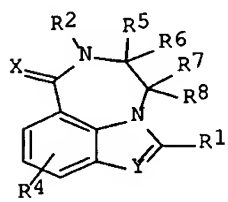


I

AB The title compds. [I; X = O, S; Y = N, CR3 (wherein R3 = halo, CN, alkyl, etc.); R1 = H, halo, CN, etc.; R2 = H, alkyl; R4 = H, halo, alkyl; R5-R8 =

H, alkyl, alkenyl, aryl, etc.] which are poly(ADP-ribosyl)transferase inhibitors, and are useful in treating cancers and in ameliorating the effects of stroke, head trauma, and neurodegenerative disease, were prepd.

E.g., a multi-step synthesis of 1-phenyl-8,9-dihydro-7H-2,7,9a-triaza-benzo[cd]azulen-6-one [I; Y = N; X = O; R1 = Ph; R2, R4-R8 = H] was given.

Biol. data for compds. I were presented.

IT **328546-66-3P 328546-75-4P 328546-88-9P**

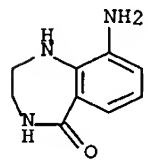
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT

(Reactant or reagent)

(prepn. of tricyclic inhibitors of poly(ADP-ribose) polymerases)

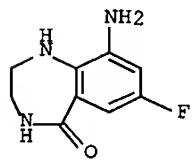
RN 328546-66-3 CAPLUS

CN 5H-1,4-Benzodiazepin-5-one, 9-amino-1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



RN 328546-75-4 CAPLUS

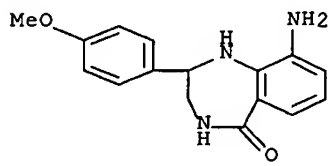
CN 5H-1,4-Benzodiazepin-5-one, 9-amino-7-fluoro-1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



RN 328546-88-9 CAPLUS

CN 5H-1,4-Benzodiazepin-5-one, 9-amino-1,2,3,4-tetrahydro-2-(4-methoxyphenyl)-

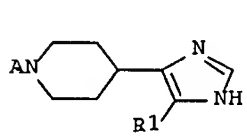
(9CI) (CA INDEX NAME)



L4 ANSWER 5 OF 12 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1995:557370 CAPLUS
DN 122:290862
TI Derivatives of imidazol-4-ylpiperidine with 5-HT3 and 5-HT4 activity, their preparation, and their use in therapy.
IN Jegham, Samir; Defosse, Gerard; Purcell, Thomas Andrew; Even, Luc
PA Synthelabo S. A., Fr.
SO Eur. Pat. Appl., 17 pp.
CODEN: EPXXDW
DT Patent
LA French
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 646583	A1	19950405	EP 1994-402114	19940923
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
	FR 2710915	A1	19950414	FR 1993-11771	19931004
	FR 2710915	B1	19951124		
	CA 2133491	AA	19950405	CA 1994-2133491	19941003
	NO 9403682	A	19950405	NO 1994-3682	19941003
	FI 9404600	A	19950405	FI 1994-4600	19941003
	AU 9474329	A1	19950413	AU 1994-74329	19941003
	JP 07179466	A2	19950718	JP 1994-238914	19941003
	ZA 9407710	A	19950810	ZA 1994-7710	19941003
	CN 1109471	A	19951004	CN 1994-117012	19941003
	HU 71120	A2	19951128	HU 1994-2832	19941003
	US 5589476	A	19961231	US 1994-317661	19941003
PRAI	FR 1993-11771		19931004		

OS CASREACT 122:290862; MARPAT 122:290862
GI



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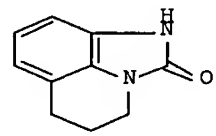
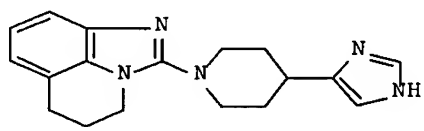


II



III

AB Title compds. I [R1 = H, straight or branched C1-6 alkyl; A = 9 specific tricyclic heterocyclic radicals with an optional phenylmethyl substituent]
and their pharmaceutical salts are claimed. The compds. are ligands of 5-HT3 and 5-HT4 receptors, and have a variety of potential uses involving
CNS and cardiovascular activities. For example, redn. of 8-quinolinamine

with Na in EtOH gave the 1,2,3,4-tetrahydro deriv., which was cyclized with urea to give dihydroimidazoquinolinone II. Treatment of II with POCl3 converted the carbonyl to the corresponding unsatd. chloride, which reacted with 4-(1H-imidazol-4-yl)piperidine in isoamyl alc. at 120.degree. to give title compd. III. The IC50 values of more active I for inhibition of [3H]-quipazine binding to rat cerebral 5-HT3 receptors were 0.01-10 nM. I also had IC50 of 0.02-2 .mu.M for inhibition of specific binding of [3H]-GR118808 to guinea pig 5-HT4 receptors.

IT **126234-17-1P**

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

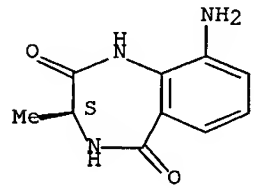
(intermediate; prepn. of imidazolylpiperidine derivs. as 5-HT3 and 5-HT4 receptor ligands)

RN 126234-17-1 CAPLUS

CN 1H-1,4-Benzodiazepine-2,5-dione, 9-amino-3,4-dihydro-3-methyl-, (S)- (9CI)

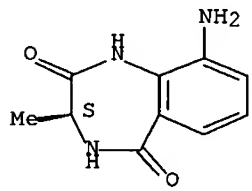
(CA INDEX NAME)

Absolute stereochemistry.

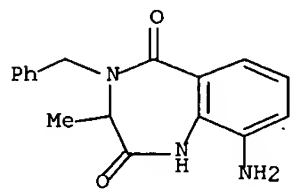


L4 ANSWER 6 OF 12 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1995:502782 CAPLUS
DN 123:112027
TI Synthesis of racemic and enantiomeric (S)-(+)-4,5,6,7-tetrahydro-5-methylimidazo[4,5,1-jk][1,4]benzodiazepin-2(1H)-one derivatives
AU Pfaendler, Hans Rudolf; Weisner, Frank
CS Inst. Organic Chem., Univ. Munich, Munich, D-80333, Germany
SO Heterocycles (1995), 40(2), 717-27
CODEN: HTCYAM; ISSN: 0385-5414
PB Japan Institute of Heterocyclic Chemistry
DT Journal
LA English
OS CASREACT 123:112027
AB Racemic and enantiomeric (S)-(+)-4,5,6,7-tetrahydro-5-methylimidazo[4,5,1-jk][1,4]benzodiazepin-2(1H)-one derivs. were prepd. using free amino acids and 3-nitroisatoic anhydride. Simultaneous redn. of two amide functions was efficiently achieved using diborane.
IT **126234-17-1P 166044-61-7P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis of racemic and enantiomeric tetrahydromethylimidazo[4,5,1-jk][1,4]benzodiazepin-2(1H)-one derivs.)
RN 126234-17-1 CAPLUS
CN 1H-1,4-Benzodiazepine-2,5-dione, 9-amino-3,4-dihydro-3-methyl-, (S)- (9CI)
(CA INDEX NAME)

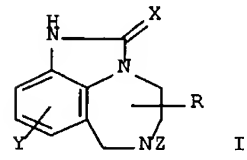
Absolute stereochemistry.



RN 166044-61-7 CAPLUS
CN 1H-1,4-Benzodiazepine-2,5-dione, 9-amino-3,4-dihydro-3-methyl-4-(phenylmethyl)- (9CI) (CA INDEX NAME)



L4 ANSWER 7 OF 12 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1995:380741 CAPLUS
DN 122:290829
TI Synthesis and Anti-HIV-1 Activity of 4,5,6,7-Tetrahydro-5-methylimidazo[4,5,1-jk][1,4]benzodiazepin-2(1H)-one (TIBO)Derivatives. 3
AU Breslin, Henry J.; Kukla, Michael J.; Ludovici, Donald W.; Mohrbacher, Richard; Ho, Winston; Miranda, Milton; Rodgers, James D.; Hitchens, T. Kevin; Leo, Gregory; et al.
CS Janssen Research Foundation, Spring House, PA, 19477, USA
SO Journal of Medicinal Chemistry (1995), 38(5), 771-93
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
GI

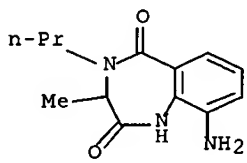


I

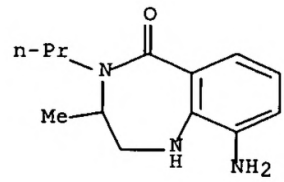
AB 4,5,6,7-Tetrahydro-5-methylimidazo[4,5,1-jk][1,4]benzodiazepin-2(1H)-ones(TIBO) (I, R = H, 5-Et, 7-Ph, etc.; X = S, O; Y = 8-Cl, 9-Cl; Z = H, 3,3-dimethylallyl, Pr, etc.) have been shown to significantly inhibit HIV-1 replication in vitro by interfering with the virus's reverse transcriptase enzyme. We describe our synthetic endeavors around 4, 5, and 7 mono- and disubstitutions of I and discuss HIV-1 inhibitory structure-activity relationships. On the basis of inhibition of HIV-1 replication in MT-4 cells, we found that 5-mono-Me-substituted analogs and 7-mono-Me-substituted analogs of I were comparable as being consistently the most active compds. Although generally less active, the 4,5,7-unsubstituted, 4-mono-substituted, cis- and trans-5,7-di-Me-substituted, and cis-4,5-di-Me-substituted analogs of I also exhibited significant activity. The remaining trans-4,5-di-Me-substituted, cis- and trans-4,7-di-Me-substituted, and all 4,5-, 5,6-, 6,7-, and 7,8-fused disubstituted analogs of I possessed no noticeable desired activity.

IT **131645-75-5P 162931-22-8P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)(synthesis and anti-HIV-1 activity of imidazobenzodiazepinones)

RN 131645-75-5 CAPLUS
CN 1H-1,4-Benzodiazepine-2,5-dione, 9-amino-3,4-dihydro-3-methyl-4-propyl-(9CI) (CA INDEX NAME)



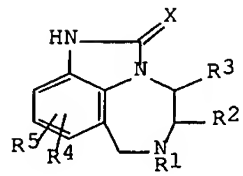
RN 162931-22-8 CAPLUS
CN 5H-1,4-Benzodiazepin-5-one, 9-amino-1,2,3,4-tetrahydro-3-methyl-4-propyl-(9CI) (CA INDEX NAME)


O
n-Pr
N
Me
N
H
NH2

L4 ANSWER 8 OF 12 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1992:235663 CAPLUS
DN 116:235663
TI Preparation of antiviral tetrahydroimidazo[1,4]benzodiazepin-2-(thio)ones
IN Kukla, Michael Joseph; Breslin, Henry Joseph; Raeymaekers, Alfons Herman Margaretha; Van Gelder, Josephus Ludovicus Hubertus; Janssen, Paul Adriaan Jan
PA Janssen Pharmaceutica N. V., Belg.
SO PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9200979	A1	19920123	WO 1991-EP1224	19910628
	W: AU, BB, BG, BR, CA, FI, HU, JP, KP, KR, LK, MC, MG, MW, NO, PL, RO, SD, SU				
	RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GN, GR, IT, LU, ML, MR, NL, SE, SN, TD, TG				
	CA 2086547	AA	19920107	CA 1991-2086547	19910628
	AU 9180683	A1	19920204	AU 1991-80683	19910628
	AU 644192	B2	19931202		
	EP 538297	A1	19930428	EP 1991-912145	19910628
	EP 538297	B1	20010919		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
	JP 05508632	T2	19931202	JP 1991-511094	19910628
	HU 68382	A2	19950628	HU 1993-11	19910628
	PL 168320	B1	19960229	PL 1991-297379	19910628
	PL 169662	B1	19960830	PL 1991-309617	19910628
	PL 169613	B1	19960830	PL 1991-309618	19910628
	AT 205848	E	20011015	AT 1991-912145	19910628
	ES 2164044	T3	20020216	ES 1991-912145	19910628
	CZ 279900	B6	19950816	CZ 1991-2065	19910704
	IL 98726	A1	19960131	IL 1991-98726	19910704
	SK 278442	B6	19970507	SK 1991-2065	19910704
	ZA 9105239	A	19930331	ZA 1991-5239	19910705
	CN 1057840	A	19920115	CN 1991-104581	19910706
	CN 1034122	B	19970226		
	NO 9204853	A	19921215	NO 1992-4853	19921215
	US 5270464	A	19931214	US 1993-42858	19930405
	US 5371079	A	19941206	US 1993-132030	19931005
	US 6201119	B1	20010313	US 1994-304951	19941017
PRAI	US 1990-549349	A	19900706		
	GB 1988-6449	A	19880318		
	GB 1989-4108	A	19890223		
	US 1989-323585	B2	19890314		
	GB 1989-20354	A	19890908		
	US 1989-406625	B2	19890913		
	US 1989-406626	B2	19890913		
	US 1990-476926	B2	19900208		
	US 1990-549777	B2	19900709		
	US 1990-583533	B2	19900917		
	US 1991-671238	B1	19910319		
	WO 1991-EP1224	A	19910628		

US 1993-42858 A3 19930405
US 1993-132030 A3 19931005
OS MARPAT 116:235663
GI



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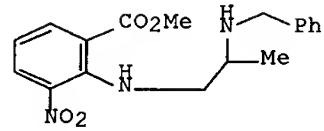
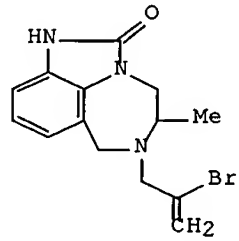


II



III

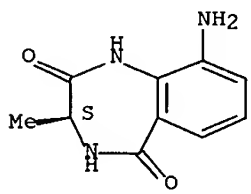
AB Title compds. [I; X = O, S; R1 = (substituted) alkenyl, cycloalkylalkyl, alkylthioalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, etc.; R2,R3 = H, alkyl; R4,R5 = H, alkyl, halo, cyano, NO2, CF3, OH, alkoxy, (alkyl)amino, alkylcarbonylamino, arylcarbonylamino], were prepd. Thus, diamine II [prepn. from Me 2-bromo-3-nitrobenzoate and (H2NCH2CHMe)NHCH2Ph given] was sapond. with aq. NaOH in Me2CHOH (82%) and the product was refluxed with SOCl2 in PhMe to give 85% 2,3,4,5-tetrahydro-3-methyl-9-nitro-4-benzyl-1H-1,4-benzodiazepin-5-one. The latter was reduced with LiAlH4 (87.6%) and the product was heated with urea at 210-220.degree. to give 11.5% imidazobenzodiazepinone deriv., which was hydrogenolyzed in HOAc over Pd/C to give 66.8% 4,5,6,7-tetrahydro-5-methylimidazo[4,5,1-jk][1,4]benzodiazepin-2(1H)-one. The latter was heated with Na2CO3, KI, and 2,3-dibromopropene in DMF to give title compd. III. I had ED50's of 0.032-0.006 .mu.g/mL against HIV-1 in MT-4 cells.

IT **126234-17-1P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as intermediate for imidazobenzodiazepinone virucide)

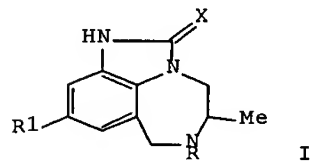
RN 126234-17-1 CAPLUS

CN 1H-1,4-Benzodiazepine-2,5-dione, 9-amino-3,4-dihydro-3-methyl-, (S)-(9CI)(CA INDEX NAME)

Absolute stereochemistry.

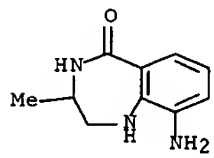


L4 ANSWER 9 OF 12 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1991:632195 CAPLUS
DN 115:232195
TI Synthesis and anti-HIV-1 activity of 4,5,6,7-tetrahydro-5-methylimidazo[4,5,1-jk][1,4]benzodiazepin-2(1H)-one (TIBO) derivatives. 2
AU Kukla, Michael J.; Breslin, Henry J.; Diamond, Craig J.; Grous, Philip P.;
Ho, Chih Y.; Miranda, Milton; Rodgers, James D.; Sherrill, Ronald G.; De Clercq, Erik; et al.
CS Janssen Res. Found., Spring House, PA, 19477, USA
SO Journal of Medicinal Chemistry (1991), 34(11), 3187-97
CODEN: JMCMAR; ISSN: 0022-2623
DT Journal
LA English
GI

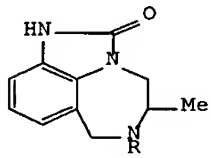


I

AB Potential anti-HIV-1 imidazo[4,5,1-jk][1,4]benzodiazepin-2(1H)-one I (R = R1 = H, X = O) analogs with variations of the five-membered urea ring were prepd. Although many different rings were synthesized to replace the cyclic urea of I, most were found to be inactive in inhibiting the replication of the HIV-1 virus in MT-4 cells. The exceptions were replacement of the urea oxygen with sulfur or selenium to give the corresponding thio- or selenoureas. These were found to be more active than the oxygen counterparts. A small series of analogs were synthesized and tested which allowed direct comparison of urea and thiourea derivs. Without exception, the latter were always more active than the former. The most active compd. (S)(+)-I (R = CH2C:CEt2, R1 = Cl, X = S) was found to inhibit the HIV-1 virus with an IC50 of 0.012 .mu.M which is comparable to that of AZT.
IT **136722-94-6**
RL: RCT (Reactant); RACT (Reactant or reagent)
(cyclocondensation of, with formamidine acetate)
RN 136722-94-6 CAPLUS
CN 5H-1,4-Benzodiazepin-5-one, 9-amino-1,2,3,4-tetrahydro-3-methyl- (9CI) (CA INDEX NAME)



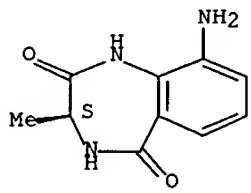
L4 ANSWER 10 OF 12 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1991:101957 CAPLUS
DN 114:101957
TI Synthesis and anti-HIV-1 activity of 4,5,6,7-tetrahydro-5-methylimidazo[4,5,1-jk][1,4]benzodiazepin-2(1H)-one (TIBO) derivatives
AU Kukla, Michael J.; Breslin, Henry J.; Pauwels, Rudi; Fedde, Cynthia L.; Miranda, Milton; Scott, Malcolm K.; Sherrill, Ronald G.; Raeymaekers, Alfons; Van Gelder, Jozef; et al.
CS Janssen Res. Found., Spring House, PA, 19477, USA
SO Journal of Medicinal Chemistry (1991), 34(2), 746-51
CODEN: JMCMAR; ISSN: 0022-2623
DT Journal
LA English
OS CASREACT 114:101957
GI



I

AB Title compds. I (R = alkenyl, alkyl, heterocycloalkyl, etc.) have been synthesized and tested for their ability to inhibit the replication of the HIV-1 virus in MT-4 cells. Two synthetic methods are described, one of which allows the synthesis of single enantiomers of the final products. A structure-activity study was done within the series of compds. to det. the optimum group for the 6-position substitution and to det. whether the activity was enantiospecific at the 5-position, which was substituted with a Me group. The best analog, (S)-(+)-I (R = CH2CH:CMe2), inhibited HIV-1 with an IC50 (conc. required to protect 50% of the cells against HIV-1-induced cytopathic effects) of 4 .mu.M, which is comparable to the activity level of DDI, a 2',3'-dideoxynucleoside-type structure undergoing clin. trials as an anti AIDS therapy.
IT **126234-17-1P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and sequential redn. and cyclocondensation with trichloromethyl chloroformate)
RN 126234-17-1 CAPLUS
CN 1H-1,4-Benzodiazepine-2,5-dione, 9-amino-3,4-dihydro-3-methyl-, (S)-(9CI)(CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 11 OF 12 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1991:62128 CAPLUS
DN 114:62128
TI Preparation of antiviral tetrahydroimidazo [1,4] benzodiazepin-2-thiones
IN Kukla, Michael Joseph; Breslin, Henry Joseph; Raeymaekers, Alfons Herman Margaretha; Van Gelder, Josephus Ludovicus; Janssen, Paul Adriaan
PA Janssen Pharmaceutica N. V., Belg.
SO Eur. Pat. Appl., 30 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 384522	A1	19900829	EP 1990-200348	19900216
	EP 384522	B1	19930113		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL				
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	AT 84534	E	19930115	AT 1990-200348	19900216
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OS MARPAT 114:62128
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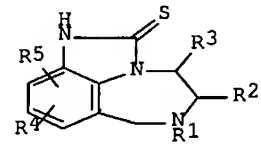


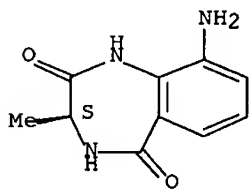
I

AB The title compds. [I; R1 = alkyl, alkenyl, alkynyl, cycloalkyl, arylalkyl, cycloalkylalkyl; R2, R3 = H, alkyl; R4, R5 = H, alkyl, halo, cyano, NO2, CF3, OH, alkoxy, amino], were prepd. Thus, a mixt. of 6-chloro-2H-3,1-benzoxazine-2,4(1H)dione and alanine Me ester hydrochloride was refluxed 10 h to give 52-5% S-7-chloro-3,4-dihydro-3-methyl-1H-1,4-benzodiazepine-2,5-dione. The latter was treated with HNO3 at 0.degree. to give the 9-nitro compd., which was converted to S-2,9-dichloro-4,5,6,7-tetrahydro-5-methyl-6-(3-methyl-2-butenyl)imidazo[4,5,6-jk]benzodiazepine, which was refluxed with thiourea in EtOH to give I (R1 = CH2CH:CMe2, R2 = Me, R3 = R4 = H, R5 = 9-Cl) (II).
II had an ED50 of 0.0005 .mu.g/mL for inhibition of HIV-1 cytopathic effect on MT-4 cells.

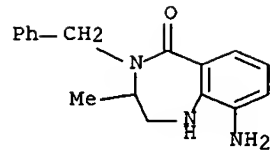
IT **126234-17-1P 126262-73-5P 131645-75-5P 131645-84-6P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as virucide intermediate)

RN 126234-17-1 CAPLUS
CN 1H-1,4-Benzodiazepine-2,5-dione, 9-amino-3,4-dihydro-3-methyl-, (S)- (9CI)
(CA INDEX NAME)

Absolute stereochemistry.



RN 126262-73-5 CAPLUS
CN 5H-1,4-Benzodiazepin-5-one, 9-amino-1,2,3,4-tetrahydro-3-methyl-4-(phenylmethyl)- (9CI) (CA INDEX NAME)



RN 131645-75-5 CAPLUS
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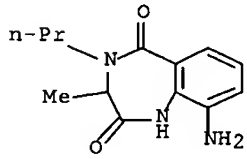

RN 131645-84-6 CAPLUS
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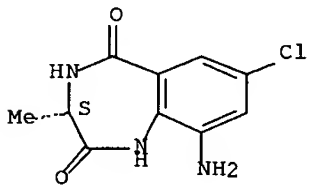
Absolute stereochemistry.



L4 ANSWER 12 OF 12 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1990:179038 CAPLUS
DN 112:179038
TI Preparation and formulation of antiviral tetrahydroimidazo[1,4]benzodiazepin-2-ones
IN Raeymaekers, Alfons H. M.; Van Gelder, Josephus L. H.; Kukla, Michael J.; Breslin, Henry J.; Janssen, Paul A. J.
PA Janssen Pharmaceutica N. V., Belg.
SO Eur. Pat. Appl., 21 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 4

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PI	EP 336466	A1	19891011	EP 1989-200575	19890308
	EP 336466	B1	19921230		
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	AU 617435	B2	19911128		
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	US 1990-583533	B2	19900917
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OS MARPAT 112:179038

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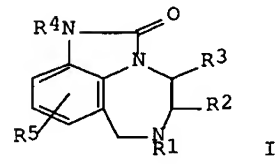

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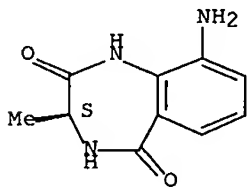
AB Title compds. I [R1 = H, C1-8 alkyl, C3-6 alkenyl, C3-6 alkynyl, C1-6 alkylcarbonyl, C3-6 cycloalkyl, substituted C1-6 alkyl; R2 = H, C1-6 alkyl, C3-6 alkenyl; R3 = H, C1-6 alkyl; R4 = H, (un)substituted C1-6 alkyl, C1-6 alkoxycarbonyl, C1-6 alkylcarbonyls, C3-6 alkenyl, C3-6 cycloalkyl, C5-6 cycloalkenyl; R5 = H, C1-6 alkyl, halo, (un)substituted Ph] useful as antiviral agents (no data) are prepd. 9-Amino-2,3,4,5-tetrahydro-3-methyl-4-(phenylmethyl)-1H-benzodiazepin-5-one (prepn. given)
and urea were heated to 210-220.degree., the reaction mixt. boiled with HCl, alkalized with NH4OH to give 11.5% I (R1 = PhCH2; R2 = Me; R3-R5 = H).

IT **126234-17-1P 126262-73-5P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as intermediate for tetrahydroimidazobenzodiazepinone virucides)

RN 126234-17-1 CAPLUS

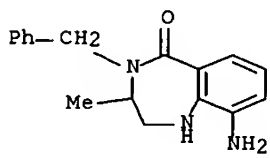
CN 1H-1,4-Benzodiazepine-2,5-dione, 9-amino-3,4-dihydro-3-methyl-, (S)-(9CI)(CA INDEX NAME)

Absolute stereochemistry.



RN 126262-73-5 CAPLUS

CN 5H-1,4-Benzodiazepin-5-one, 9-amino-1,2,3,4-tetrahydro-3-methyl-4-(phenylmethyl)- (9CI) (CA INDEX NAME)



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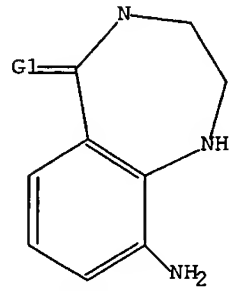

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L4             12 S L3


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DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
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